RESEARCH ARTICLE

A Comparison of the Therapeutic Effect of Tramadol and Meperidine for Treatment of Shivering after Spinal Anesthesia in Elective Caesarean Section

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Background: In most operating and recovery rooms, shivering is controlled by the use of humidifiers, warming blankets, and inhalation of humidified heated oxygen. However, pharmacological control is an effective alternative treatment modality. This study was designed to compare the efficacy of tramadol versus meperidine in the treatment of shivering after spinal anesthesia.

Methods: In a double-blind randomized clinical trial, we studied 70 obstetric patients with ASA class I or II who had shivering following spinal anesthesia (SA) with 0.5% bupivacaine. All patients were randomly allocated to one of the two groups receiving tramadol 0.5 mg/kg (group T, n = 35), or meperidine 0.5 mg/kg (group M, n = 35). The onset of cessation of shivering, the efficacy of agents for treatment of shivering, hemodynamic variables, sedation score, pruritus, nausea and vomiting were assessed.

Results: Shivering ceased after 2.57±2.26 and 6.24±4.76 minutes in group T and group M respectively (p=0. 03). The differences before and after injection of meperidine for the heart rate, respiratory rate and arterial oxygen saturation were significant (p<0.001). Nausea and vomiting occurred significantly more frequently in the meperidine group compared to the tramadol group (p<0.001).

Conclusion: Tramadol is a more effective agent than meperidine in the treatment of post spinal shivering, with lower early side effects in obstetric patients.

Keywords: spinal anesthesia; tramadol; meperidine; shivering

Shivering is an unpleasant and frequent complication in the postoperative period [1]. It may interfere with monitoring of electrocardiogram, blood pressure, and pulse oximetry [2]. In patients with post anesthesia shivering, left ventricular systolic work index is increased and oxygen consumption may be increased by 200% to 500% [3]. Thus, in patients with decreased myocardial reserve, shivering may further compromise myocardial function. Shivering may also increase intraocular and intracranial pressures, and may also contribute to increased wound pain [4]. The possible mechanisms of shivering after spinal anesthesia in parturients result from central thermoregulation disturbance [5]. Shivering may be justified as a thermoregulatory response to hypothermia that occurs during operation and presents with tonic or clonic patterns [6]. Equipment to maintain normothermia is effective in preventing shivering, but may be expensive and is not practical in all settings [7]. Pharmacological agents remain the most popular mode of treatment for shivering. Many agents have been used to eliminate postoperative shivering such as meperidine, doxapram, tramadol, ketanserin, clonidine, propofol, physostigmine and nefopam, dexamethasone, magnesium sulfate, and fentanyl [8-10]. Among the opioids, mepridine has been found to be the most efficacious. Meperidine controlled shivering better than equal analgesic doses of other pure μ-opioid agonists such as fentanyl, alfentanil, sufentanil, or morphine, and unlike them the antishivering effects of meperidine were reversed by large-doses of naloxone [11]. Accordingly, the antishivering effect of meperidine may be mediated in part by activation of none μ-opioid receptors. However, meperidine probably acts directly on the thermoregulatory center [12]. Disadvantages of meperidine are excessive sedation, respiratory depression and postoperative nausea and vomiting, which may be induced with previously administered opioids or anesthetics. Tramadol is effective in the treatment of postanesthetic shivering [12]. Tramadol producees weak sedation effect and present low respiratory depression, thus, it can be used safely in parturients [13]. It was shown that tramadol inhibits the neuronal reuptake of norepinephrine and 5-hydroxytrypamine, facilitates 5-hydroxytrypamine release, and activates μ-opioid receptors

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[14]. Each of these actions is likely to influence the thermoregulatory control [15]. However, tramadol had only slight thermoregulatory effect and thus, it is unlikely to provoke hypothermia [16]. The main opioid effect of tramadol is mediated via the μ receptor [17]. Moreover, the antinociceptive effects of tramadol were significantly decreased by α2-adrenoceptor antagonists [18]. Also, it was identified that tramadol is similar to clonidine, a partial α2-adrenoceptor agonist and could be useful in the treatment of postoperative shivering [19]. Delaunay showed that clonidine reduced the thermoregulatory thresholds for both vasoconstriction and shivering [19]. Tramadol may induce its antishivering effects via both-opioid receptor and α2-adrenergic agonist mechanisms. The interaction of opioid and α2-adrenoceptor mechanisms working in a complementary or synergistic manner and produce antishivering effects [20]. Recent studies have investigated the efficacy of tramadol in the management of perioperative of shivering [21]. Some of the studies have shown that tramadol was better than meperidine for treatment of perioperative shivering [22-23]. The aim of this study was to compare the anti-shivering effects and the accompanying early side effects of tramadol and meperidine after spinal anesthesia in parturients.

Methods

In a double blind, randomized clinical trial with approval of ethic committee of our hospital and informed written consent, we studied 70 obstetric patients with ASA physical status I-II who were candidates for elective cesarean section and developed shivering following spinal anesthesia. The severity of shivering was graded on a scale of 0 to 4 that had been validated by Crossley and Mahajan [24] (zero = no shivering, 1= peripheral vasoconstriction, but no visible shivering, 2 = muscular activity in only one muscle group, 3 = muscular activity in more than one muscle group but not generalized shivering, 4 = shivering involving the whole body). Only parturients who developed Grade 3 or 4 shivering for at least 3 min were included. The exclusion criteria were hyperthyroidism, cardiopulmonary disease, hemodynamic instability, patients with ASA class 3 or 4 and a known history of alcohol or substance abuse. The temperature of the operating room was maintained at 23°C. Standard monitoring, including continuous ECG, heart rate, non-invasive arterial blood pressure, and continuous pulse oximetry (Novin S1800, Iran) was used during surgery. All patients recived preloading with 5 ml/kg ringer lactate and then underwent spinal anesthesia with the midline approach at the L3-L4 interspace using a 27-Gauge spinal needle. After free CSF flow had been observed, 10 mg hyperbaric bupivacaine 0.5% (Marcaine Spinal Heavy, Astra, Sweden) was injected through the needle. Then, patients were immediately turned to supine. Hypotension was defined as a systolic blood pressure less than 90 mmHg or a decrease of more than 25% from the baseline of mean arterial pressure at the first 30 min after spinal anesthesia. The hypotension episodes were treated with a loading dose of intravenous fluids and an intravenous bolus of ephedrine 5–10 mg. Of the 70 parturients who shivered after spinal anesthesia and requested anti-shivering treatment were assigned randomly according to a computer generated random number table to two groups; group T (n = 35) who received 0.5 mg/kg tramadol hydrochloride and group M (n = 35) that received 0.5 mg/kg meperidine. The dosage of tramadol and meperidine was chosen according to previous studies [25]. Our surgeons, anesthesiologists and research physicians were unaware of the allocation of the study participants. Drug efficacy was assessed on the basis of a sustained decrease in the grade of shivering. The perioperative side-effects, including changes in hemodynamic status, sedation score based on the Ramsay Sedation Scale, pruritus, nausea and vomiting were assessed. Statistical analysis was performed with the software SPSS. Nonparametric data were analyzed using the t-test. Categorical data were analyzed using the $\chi 2$ test. Values are reported as mean ± SD. A p-value of <0.05 was considered statistically significant.

Results

The baseline characteristics and clinical data were comparable between the two groups (Table1). None of our cases in both groups were excluded during our study. The shivering ceased 2.57±2.26 minutes and 6.24±4.76 minutes after administration of tramadol and meperidine respectively (p=0. 03). The efficacy of anti-shivering effect was not statistically different between two groups (91.4% and 82.8% after 5 minutes of spinal anesthesia and 97.1% and 88.5% after 10 minutes of spinal anesthesia in tramadol and meperidine group respectively (p=0. 34). Sedation score within 30 minutes was similar for both groups (p=0. 051). Moreover, there were no significant differences in systolic (p=0. 28) and diastolic (p=0. 28) blood pressures 5, 10 and 30 minutes after spinal anesthesia between the two groups. However, there was a significant difference in heart rate ($p<0.001$), arterial oxygen saturation ($p<0.001$) and respiratory rate ($p<0.001$) within 30 minutes after spinal anesthesia between the two groups. Nausea and vomiting occurred significantly more frequent in the meperidine group compared to the other group ($p<0.001$), but pruritus was not significantly different between the two groups (p=0. 51) (Table 2).

Discussion

The results of this study support the results of other studies indicating that tramadol is effective in the treatment of postanaesthetic shivering, and show that the time of an end of shivering is significantly earlier than after meperidine administration. The efficacy of tramadol in the treatment of shivering after spinal anesthesia in this study was similar to the results of previous studies [15]. In a double blind, randomized clinical trial study of pregnant women who were candidates for elective caesarean section, it was shown that the control of shivering with tramadol was better than meperidine like in our study [22, 26-31]. In another study, ceasing of shivering after tramadol was faster than meperidine, and also with fewer side effects [7]. Also, Bhattacharya reported that the tramadol was better than meperidine for control of postoperative shivering [13]. In a clinical trial on 50 patients undergoing orthopedic surgery, the time for control of shivering after surgery with tramadol was faster than meperidine and arterial oxygen saturation in trmadol group was significantly higher than in the meperidine group [32].

Table 1- Baseline characteristics and clinical data

Variables	Tramadol Group	Meperidine Group	P Value
Age (yrs)	27.4±12.4	26.8±10.8	0.47
Weight (Kg)	65.8±14.8	68.2±12.4	0.34
Heart rate	96.4±18.8	93.9±20.6	0.08
Systolic blood pressure (mmHg)	103.5±9.2	108±10.5	0.29
Diastolic blood pressure (mmHg)	64.7±8.4	66±8.5	0.43
Respiratory rate	14.6±2.67	14.9±1.15	0.78
Arterial O2 saturation	97±1.1	97.5±0.74	0.34
Upper sensory spread of spinal anesthesia (T4)	34 (97.1%)	33(94.2%)	0.42
Onset of shivering after spinal anesthesia (min)	12.2	13.1	0.32

Table 2- Comparison of variables at 5, 10 and 30 minutes after administration of tramadol and meperidine for treatment of post spinal shivering

Variables	Time	Tramadol Group	Meperidine Group	P Value
Sedation score (mean)	3 min	10±2	18±2	0.051
	10 min	11±3	18±4	
	30 min	10±4	16±4	
Systolic blood pressure (mean)	3 min	103.8±7.4	109.7±7.8	0.28
	10 min	105±10.2	110±8.4	
	30 min	104±8.6	108±10.2	
Diastolic blood pressure (mean)	3 min	64.6±6.8	67.7±8	0.28
	10 min	75.2±4.2	72.8±4.4	
	30 min	74.2±6.4	72.6±6.8	
Heart rate (mean)	3 min	90.8±15.1	102.3±17.6	<0.001
	10 min	95.4±12.8	105±14.6	
	30 min	92.5±10.4	104±15.7	
Respiratory rate (mean)	3 min	14.6±1.78	13.1±1.25	<0.001
	10 min	14.8±2.6	12.6±1.8	
	30 min	14.6±2.4	12.8±2	
Arterial O2 saturation (mean)	3 min	97.2±1.5	95.7±1.52	<0.001
	10 min	98.2±1.8	94.2±1.64	
	30 min	98.4±1.2	94.6±1.24	
Nausea and vomiting	Within 30 min	4 (11.4%)	19 (54.3%)	<0.001
Pruritus	Within 30 min	Zero	1 (2.9%)	0.51

In another study, the effects of amitriptyline, meperidine and tramadol in the treatment of shivering after epidural anesthesia in pregnant women were investigated. It was found that tramadol and meperidine were better than amitriptyline in the treatment of shivering,but the respiratory depression risk was greater with meperidine and nausea and vomiting were similar between the two groups [33]. However, in a clinical trial on 40 patients who were shivering after spinal anesthesia, the patients were randomly divided into two groups receiving 0.5mg/kg meperidine or 0.5mg/kg tramadol after shivering. Results showed that response to treatment was similar in both groups, and also, there was not significant difference in respiratory index, level of consciousness, nausea and vomiting between the two groups [34]. Tramadol's mechanism of action in the treatment of shivering is not clearly known. About the mechanisms of tramadol in shivering control it can be noted that it has its effect through inhibition of norepinephrine and dopamine and thus facilitates the release of serotonin [16]. Tramodol is a racemic mixture composed of two isomers, R and L having different activity spectrum. The R isomer showed weak 5-OH triptamine inhibition re-uptake of noradrenaline and increased its excertion. But, the L isomer strongly inhibits re-uptake of noradrenaline [35-36]. Difference in their performance supports the view that the effect of tramadol in the elimination of shivering may be related to noradrenergic activity. In our study, systolic and diastolic arterial blood pressures were similar between the two groups, but heart rate, arterial oxygen saturation, respiratory rate and nausea and vomiting were significantly different between the two groups. It was shown that tramadol with doses of 0.5-1 mg/kg prevented post anesthetic shivering and did not affect on the arterial blood pressure [37]. Moreover, previous studies identified that use of 1 mg/kg tramadol for the treatment of shivering after epidural and general anesthesia showed no clear change in the heart rate [38-39]. It was shown that the most important problem in tramadol use was nausea and vomiting [36]. Previous studies that evaluated the efficacy of tramadol in the treatment of post anesthesia shivering observed that nausea and vomiting increased with 1 and 2 mg/kg tramadol, but the number of nausea and vomiting cases reduced through slow infusion application [37-40]. Our study observed that nausea and vomiting were less in tramadol compared to meperidine group. The reasons for this observation were the use 0.5 mg/kg tramadol and also slow infusion of tramadol in our study. In conclusion, tramadol in a dose of 0.5 mg/kg is a more effective agent for the treatment of post spinal shivering than meperidine 0.5 mg/kg, and it is not associated with hemodynamic disturbances, excessive sedation or other side-effects and could be recommended in parturients who shiver after spinal anesthesia.

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